

## Biventricular Pacing

# Atrioventricular Pacing Improves Exercise Capacity in Patients With Heart Failure and Intraventricular Conduction Delay

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<b>OBJECTIVES</b>	We sought to assess the efficacy of biventricular pacing with respect to both peak and submaximal measures of exercise in patients with New York Heart Association class III heart failure (HF) and intraventricular conduction delay in a randomized, blinded study.
<b>BACKGROUND</b>	Submaximal and maximal changes in exercise capacity need evaluating in this patient population with this novel therapy.
<b>METHODS</b>	Graded exercise and 6-min walk tests were performed in patients randomized to three months each of active (atrio-biventricular) and inactive pacing. Minute ventilation (VE), oxygen uptake ( $\text{VO}_2$ ), ventilated carbon dioxide ( $\text{VCO}_2$ ) and heart rate were measured in patients achieving a respiratory quotient $>1$ ( $n = 30$ ). Oxygen pulse, anaerobic threshold (AT) and ventilatory efficiency ( $\text{VE}/\text{VCO}_2$ ) were calculated.
<b>RESULTS</b>	Active biventricular pacing increased peak $\text{VO}_2$ ( $15.8 \pm 4.3$ vs. $14.4 \pm 4.6$ ml/kg/min, $p = 0.02$ ), exercise time ( $501 \pm 223$ s vs. $437 \pm 233$ s, $p < 0.001$ ) and oxygen pulse ( $9.3 \pm 2.8$ vs. $8.1 \pm 3.1$ ml/beat, $p < 0.01$ ) compared with inactive pacing. The submaximal measures of exercise capacity significantly increased with active pacing: AT ( $11.2 \pm 4.1$ ml/kg/min vs. $9.5 \pm 2.3$ ml/kg/min, $p = 0.02$ ) and 6-min walk ( $414 \pm 94$ m vs. $359 \pm 94$ m, $p = 0.001$ ). Minute ventilation/ventilated carbon dioxide improved ( $32 \pm 9$ vs. $36 \pm 11$ , $p = 0.03$ ) with normalization of the $\text{VE}/\text{VCO}_2$ slope in 59% of patients (chi-square test, $p = 0.002$ ) with active pacing.
<b>CONCLUSIONS</b>	Biventricular pacing may improve maximal and submaximal exercise capacity in patients with advanced HF and intraventricular conduction delay. (J Am Coll Cardiol 2003;41:582–8) © 2003 by the American College of Cardiology Foundation

Patients with severe heart failure (HF) experience considerable disability despite important advances in medical therapy (1–4). Simultaneous pacing of the left ventricle (LV) and right ventricle (biventricular pacing) has been proposed as an advantageous electrical therapy that, in patients with severe HF and intraventricular conduction delay (5), improves ventricular coordination and hemodynamics (6–9). The feasibility of permanent implantation has been proven, and clinical improvement has been suggested in observational studies (10).

The Multisite Stimulation in Cardiomyopathy Study (MUSTIC) is a multicenter study that compared active biventricular pacing with no pacing in a prospective, randomized, single-blind, crossover study. The primary and secondary end points, including peak oxygen uptake ( $\text{VO}_2$ ) with exercise, have been recently published with an Appen-

dix list of participants of the MUSTIC study (11). Patients with severe HF tend to perform daily tasks that are more related to submaximal measures of exercise. Information from metabolic measures during submaximal exercise—anaerobic threshold (AT) and ventilatory response to exercise—may be more appropriate than maximal measures when comparing the efficacy of any given therapeutic strategy. The slope of minute ventilation (VE) per unit of ventilated carbon dioxide ( $\text{VCO}_2$ ), a measure of ventilatory drive, is also a powerful index of prognosis for patients with moderate to severe HF—the higher the slope the worse the outcome, generally (12,13). We studied the detailed cardiopulmonary exercise data in the patients from the MUSTIC study to compare the effect of active biventricular pacing with no pacing on both maximal and submaximal measures of exercise.

## METHODS

**Patient population.** Patients included in this study were in New York Heart Association (NYHA) class III HF, receiving optimal medical therapy at the maximal tolerated dose, and in a stable condition for  $>1$  month (no NYHA class changes, no hospitalization for HF, and no change in

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#### Abbreviations and Acronyms

AT	= anaerobic threshold
CPET	= cardiopulmonary exercise test
HF	= heart failure
HR	= heart rate
LV	= left ventricle, ventricular
MUSTIC	= Multisite Stimulation in Cardiomyopathy study
NYHA	= New York Heart Association
QOL	= quality of life
VCO <sub>2</sub>	= ventilated carbon dioxide
VE	= minute ventilation
VO <sub>2</sub>	= oxygen uptake

medication). Patients had an echocardiographic LV end diastolic diameter >60 mm, a distance of <450 m in the 6-min walk test, and an ejection fraction <35% on angiography or scintigraphy. Patients had to be in sinus rhythm with an intrinsic QRS duration of >150 ms. Informed consent was obtained from the patients, and local ethics approval was obtained at each investigational center.

Patients were excluded if they were suspected of having acute myocarditis or had hypertrophic or restrictive cardiomyopathy, a systolic blood pressure >160 mm Hg or diastolic blood pressure >95 mm Hg despite treatment, symptomatic or sustained ventricular tachycardia, unstable coronary symptoms (angina or myocardial infarction) within three months or a planned revascularization, correctable valve disease, inability to walk, or a conventional pacemaker indication.

**Study design.** The MUSTIC study design was a randomized, crossover phase design comparing biventricular stimulation with no ventricular stimulation (11). Treatment order was randomized according to a complete randomized block design. Programming was randomized to DDD biventricular or VVI 40 and changed to the alternative program mode at the crossover stage between phases 1 and 2 in each individual. Cardiopulmonary exercise testing (CPET), 6-min distance walked, and quality of life (QOL) evaluation were performed at enrollment (to familiarize patients with the tests), randomization (2 weeks after implantation), phase 1 (12 weeks after randomization) and phase 2 (24 weeks after randomization). Patients were blinded to the programmed pacemaker settings. During the crossover phases, changes in diuretic therapy were permitted if required; but dosage was constant for other medications, and no new drug for congestive HF was added during the study.

**Implantation and programming of pacemaker.** Before lead placement, coronary sinus venography was undertaken to define the anatomy. Left ventricular lead 2187 or 2188 (Medtronic Inc., Minneapolis, Minnesota), right ventricular and right atrial leads were introduced into either the cephalic or subclavian veins. Optimal LV lead placement was mid-lateral in a wedged position. Other locations (antero-lateral, posterior) were acceptable. The right ven-

tricular lead was anatomically as far as possible from the LV lead. Either InSync 8040 (Medtronic) or Chorum MSP (ELA Medical, Montrouge, France) was implanted. The pacemaker was programmed to a basic rate of 40 beats/min and upper limit 85% of the age–gender maximum predicted heart rate (HR). The atrioventricular delay was optimized using echo Doppler, selecting optimal filling time and aortic outflow velocity time integral. Active pacing was defined as pacing configuration DDD biventricular and inactive pacing defined as pacing configuration VVI 40.

**Outcomes measured.** Each patient performed a supervised CPET to maximum tolerance either on a treadmill or cycloergometer according to the facilities at each center. Graded exercise bicycle testing was performed on an electromagnetically braked cycle using a 20 W start and 10 W min incremental increase. Treadmill exercise testing was performed using a modified Bruce protocol. All tests in a given patient were performed with the same equipment and protocol in each phase of the study. A light meal could be eaten up to 3 h before the test. Gas exchange measurements (Medical Graphics Corporation, St. Paul, Minnesota) were made during 3 min of rest, followed by progressively increasing work rate exercise and 5 min of recovery. Pulse oximetry, HR, 12-lead ECG, and cuff blood pressure were monitored and recorded. Criteria for termination were intense dyspnea, exhaustion, angina pectoris, fall in blood pressure, non-sustained or sustained ventricular tachycardia, poorly tolerated atrial tachyarrhythmias, or achievement of maximal predicted HR.

Minute ventilation, VO<sub>2</sub>, VCO<sub>2</sub> and other exercise variables were computer calculated breath by breath, interpolated second by second, and averaged over 10-s intervals (14). Data were collected from all investigational centers and analyzed centrally to avoid center bias and to standardize interpretation. Each test was coded so that the analyzers were blinded to the mode of pacing. For the exercise data to be analyzed, detailed 10 s plotted data had to be available, and only patients achieving a respiratory quotient >1 were included.

The achieved peak VO<sub>2</sub> results were expressed as ml/kg/min. The O<sub>2</sub> pulse is the quotient of the VO<sub>2</sub> (in ml) over HR and is determined by stroke volume and the arterio-venous (AVO<sub>2</sub>) difference (14). The AT was determined by plotting VCO<sub>2</sub> against VO<sub>2</sub> (V slope method) (15) and then plotting VE/VCO<sub>2</sub> with VO<sub>2</sub> (dual criteria AT) (14) if needed. The results of the AT were expressed as the value of VO<sub>2</sub>, in ml/kg/min, at which the AT was reached. The VE/VCO<sub>2</sub> slope was calculated as the slope of the regression line relating VE to VCO<sub>2</sub> during exercise testing before the AT and was used as an index of the ventilatory response to exercise (14). The non-linear portion of this relationship after the onset of the acidotic drive to ventilation was excluded (16).

The 6-min walk test was performed according to the published recommendations (17,18). Baseline evaluation with a run in test followed by two further tests was

performed at 24-h intervals. At each of the other phases of assessment, two tests were performed with an interval of at least 3 h between them. The maximum difference between the two tests was 15%, and the value recorded the mean of the results of the two tests. Quality of life was assessed as part of the MUSTIC study, using the Minnesota Living With Heart Failure questionnaire at each phase of evaluation (19). The questionnaire contains 21 questions regarding patients' perceptions of the effects of HF on their daily lives. Each question is rated on a scale of 0 to 5, producing a total score between 0 and 105. The higher the score, the worse the QOL.

**Statistical analysis.** The sample size for the MUSTIC study was calculated based on an estimated 10% increase in the distance walked in 6 min with active pacing. For a study with a 95% confidence level and 95% power, the total sample size needed was estimated to be 22 patients. Patients acted as their own controls. Standard equations were used to predict actual and percent-predicted values for CPET measures (14). Period and crossover effects were checked before the efficacy of treatment was evaluated. The a priori design of this study was intended to compare measures between inactive and active pacing; therefore, two-tailed paired Student *t* tests were used. Data are presented as mean  $\pm$  standard deviation. Software used was SPSS version 9 (SPSS Inc., Chicago, Illinois). A significant change was defined as an  $\alpha$  of  $p < 0.05$ . Simple individual linear regression analyses were performed by the Pearson correlation coefficient (*r*) between individual variables.

## RESULTS

**Patient enrollment and characteristics.** Sixty-seven patients from 16 centers were enrolled into the MUSTIC study (11). Of those, five patients died before completing the crossover phases, seven had technical difficulties with pacemaker implantation, four withdrew their consent, and three were withdrawn because of the development of an exclusion criterion. Forty-eight patients completed the crossover phases. In six patients complete exercise data sets were not available, and in seven patients inadequate studies had been performed for one or more of the four phases of the study. Therefore, detailed 10-s interpretable plotted data were available for analysis in 35 patients. Only patients with a respiratory quotient  $>1$  at peak exercise in every phase, indicating satisfactory exercise effort, were then included ( $n = 30$ ). Sixteen patients were randomized to the first three months active then inactive pacing, and 14 patients to the first three months inactive then active pacing. All the patients terminated exercise because of either dyspnea or exhaustion.

Twenty-five of the patients analyzed were male. The mean age was  $64 \pm 10$  years (range 38 to 79). All were in NYHA class III HF. Baseline QRS duration was  $173 \pm 18$  ms, LV end diastolic diameter  $73 \pm 11$  mm, and LV ejection fraction  $23 \pm 8\%$ . Sixteen patients had idiopathic,

and 14 ischemic, etiology for HF. Drug treatment was loop diuretic (100%), angiotensin-converting enzyme inhibitor or angiotensin receptor blocking agent (96%), digoxin (40%), beta-blocker (37%), amiodarone (30%), and spironolactone (30%). The mean dosage of each drug was the same at baseline and at each assessment. At randomization, the peak exercise measures were peak  $\text{VO}_2$   $14.3 \pm 4.0$  ml/kg/min, exercise time  $432 \pm 190$  s, respiratory quotient  $1.14 \pm 0.10$ , HR  $125 \pm 24$  beats/min. Submaximal measures of exercise were AT  $9.8 \pm 3.5$  ml/kg/min, 6-min walk distance  $366 \pm 79$  and  $\text{VE}/\text{VCO}_2$   $40 \pm 12$ .

**Measures of peak exercise.** Individual changes in peak measures of exercise between active biventricular pacing and inactive pacing are shown in Table 1. The peak  $\text{VO}_2$  was significantly increased at the end of the active pacing phase compared with the end of the inactive phase ( $15.8 \pm 4.3$  ml/kg/min vs.  $14.4 \pm 4.6$  ml/kg/min,  $p = 0.02$ ). An improvement was seen in the peak  $\text{VO}_2$  in 24 of 30 patients with active pacing compared with inactive pacing. At the end of the inactive phase, the predicted peak  $\text{VO}_2$  was  $<40\%$  of the predicted peak  $\text{VO}_2$  in five patients, and this improved with biventricular pacing to only one patient with a peak  $\text{VO}_2$   $<40\%$  of that predicted (chi-square test,  $p < 0.05$ ). The maximum  $\text{O}_2$  pulse ( $\text{VO}_2/\text{HR}$ ) was significantly improved between the inactive phase and active pacing phase, from  $8.1 \pm 3.1$  ml/beat to  $9.3 \pm 2.8$  ml/beat,  $p = 0.002$ . The exercise time was significantly increased at the end of the active pacing phase compared with the end of the inactive phase ( $501 \pm 223$  s vs.  $437 \pm 233$  s,  $p < 0.001$ ). Change in exercise time correlated with change in peak  $\text{VO}_2$  ( $r = 0.57$ ,  $p = 0.001$ ).

**Measures of submaximal exercise.** The AT significantly increased from  $9.5 \pm 2.3$  ml/kg/min at the end of the inactive pacing phase to  $11.2 \pm 4.1$  ml/kg/min at the end of the active pacing phase,  $p = 0.014$  (Fig. 1). An improvement in AT was observed in 23 of 28 (82%) patients, Table 2. Only 10 patients reached an AT in excess of 40% of the maximum predicted  $\text{VO}_2$  during the inactive phase. This increased to 18 patients achieving an AT in excess of 40% of the maximum predicted  $\text{VO}_2$  with pacing (chi-square test,  $p = 0.03$ ). No patients reached an AT in excess of 50% of the maximum predicted  $\text{VO}_2$  during the inactive phase, compared with 12 patients with biventricular pacing. Six-minute distance walked showed a significant increase between the actively paced and inactive phases (active  $414 \pm 94$  m vs. inactive  $359 \pm 94$  m,  $p = 0.001$ ), Figure 1. The change between the active and inactive phases in 6-min walk distance correlated with the change in AT ( $r = 0.53$ ,  $p = 0.004$ ).

The  $\text{VE}/\text{VCO}_2$  slope (below the AT) was significantly lower (that is, ventilatory efficiency increased) at the end of the active pacing phase compared with the end of inactive phase ( $32 \pm 9$  vs.  $36 \pm 11$ ,  $p = 0.03$ ), Figure 1. Seventeen of the patients had a  $\text{VE}/\text{VCO}_2$  slope  $\geq 30$  (above normal) in the inactive phase, compared with seven patients  $\geq 30$  with biventricular pacing (chi-square test,  $p = 0.002$ ). The

**Table 1.** Measures of Peak Exercise During Active and Inactive Pacing in Each Individual Patient

Pt	Inactive				Active			
	Peak VO <sub>2</sub> , m/kg/min	ET, s	HR, beats/min	RQ	Peak VO <sub>2</sub> , m/kg/min	ET, s	HR, beats/min	RQ
1	13.5	245	131	1.58	13.6	269	120	1.75
2	10.8	195	107	1.01	10.9	287	104	1.18
3	16.8	497	108	1.08	13.7	480	88	1.13
4	15.2	366	113	1.09	16.4	325	89	1.04
5	28.5	170	82	1.11	28.8	205	92	1.12
6	16.0	330	82	1.07	21.5	660	92	1.17
7	13.5	429	104	1.14	14.2	411	141	1.18
8	13.8	512	110	1.10	15.0	567	125	1.01
9	20.3	420	136	1.22	22.4	541	148	1.27
10	12.9	141	111	1.24	17.0	381	135	1.66
11	13.8	465	133	1.05	15.6	480	114	1.04
12	13.4	800	161	1.20	15.2	640	129	1.10
13	9.9	197	129	1.13	11.7	168	116	1.06
14	22.6	286	106	1.41	20.1	277	111	1.32
15	13.2	377	148	1.14	18.6	507	138	1.34
16	14.0	745	133	1.04	15.2	785	127	1.04
17	20.8	339	129	1.29	17.7	471	119	1.08
18	11.8	894	125	1.01	15.3	867	135	1.03
19	11.6	600	133	1.10	16.8	720	133	1.07
20	11.1	353	125	1.18	11.5	496	113	1.14
21	8.9	191	98	1.34	9.2	211	110	1.10
22	10.4	270	98	1.08	12.1	390	108	1.08
23	11.4	730	157	1.08	15.0	928	163	1.13
24	8.9	495	133	1.31	7.5	516	100	1.60
25	14.3	330	101	1.14	16.4	373	109	1.18
26	22.7	661	110	1.11	15.0	689	129	1.12
27	17.6	259	166	1.29	19.1	315	180	1.10
28	10.8	960	158	1.01	16.0	1031	126	1.90
29	13.2	840	175	1.04	21.5	840	145	1.21
30	11.2	410	150	1.09	10.8	470	109	1.10
Mean	14.4	437	123	1.20	15.8	501	123	1.16
p value					0.024	0.001	NS	NS

ET = exercise time, Pt = patient, RQ = respiratory quotient

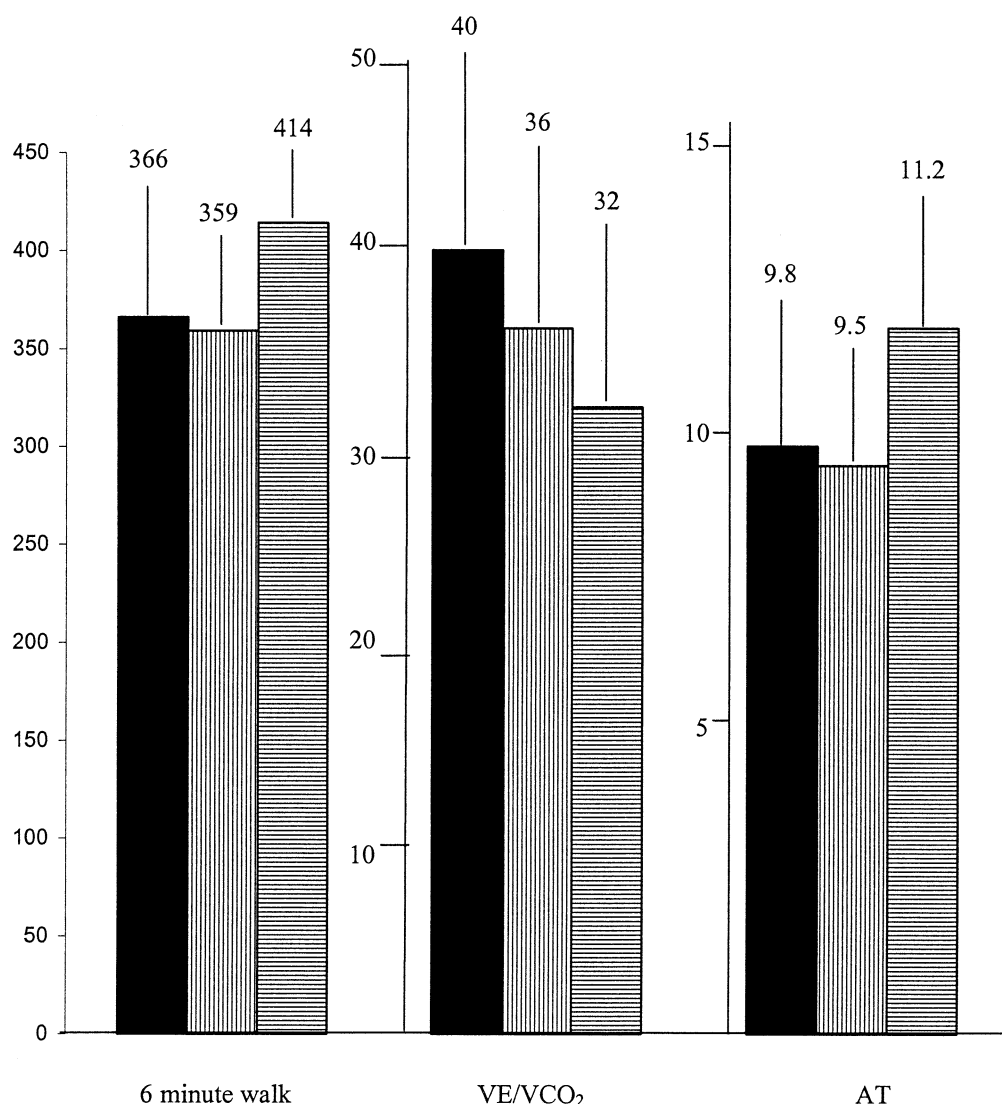
change in VE/VCO<sub>2</sub> correlated with change in exercise time ( $r = -0.55$ ,  $p = 0.01$ ) between the active and inactive phases.

**QOL.** The QOL score was significantly improved during the inactive to the active phase ( $39 \pm 20$  to  $27 \pm 22$ ,  $p = 0.002$ ). A significant correlation was seen between the change in QOL and change in 6-min walk distance ( $r = -0.61$ ,  $p < 0.001$ ); a weak correlation was observed with change in peak VO<sub>2</sub> ( $r = -0.34$ ,  $p = 0.07$ ) and exercise time ( $r = -0.30$ ,  $p = 0.12$ ). In those with a large reduction in QOL score ( $>-10$ ,  $n = 15$ ) the improvement in QOL was more strongly correlated with changes in peak exercise (peak VO<sub>2</sub>  $r = -0.57$ ,  $p = 0.03$ , exercise time  $r = -0.49$ ,  $p = 0.06$ ).

## DISCUSSION

This study demonstrated that biventricular pacing in patients who are already receiving optimal medical therapy significantly increased measures of both maximal and sub-maximal exercise, extending the published findings of the MUSTIC study (11). A high concordance has been shown

between improvement in exercise capacity and symptoms, supporting the view that exercise testing is a useful adjunct in assessing the clinical response of patients with symptomatic HF to therapeutic interventions (20). Exercise levels are dependent on several factors, including patient motivation, symptomatic limitation, premature cessation of exercise due to apprehension regarding the onset of symptoms and the level of conditioning (most patients with HF are naturally deconditioned). A general improvement in daily life activities with biventricular pacing may lead to increased physical training, which helps improve the measures of exercise. Such effects, however, should be countered by the use of patients who were blinded to the phase of study, as their own controls. The importance of the design of the study to accurately assess changes in exercise was highlighted by a comprehensive review of studies of angiotensin-converting enzyme inhibitors and exercise capacity (20). Our protocol followed the standards recommended, which include a follow-up period of at least 12 weeks and a consistent method of exercise testing for the individual patient throughout the study. The crossover design with patients



**Figure 1.** Comparison of measures of submaximal exercise during active and inactive pacing. Significant increases were observed in the distance walked in 6 min (meters,  $p = 0.001$ ) and anaerobic threshold (AT, ml/kg/min,  $p = 0.02$ ) during active pacing. A significant improvement was observed in the minute ventilation/ventilated carbon dioxide (VE/VCO<sub>2</sub>,  $p = 0.03$ ). **Black bars** = randomization; **vertically lined bar** = inactive pacing; **horizontally lined bar** = active pacing.

serving as their own controls effectively doubles the power of the study and reduces the number of centers entered, leading to greater uniformity in application of CPET. Most of the drug treatments for HF have resulted in some improvement in exercise capacity (21–25). The effect of biventricular pacing—to increase peak VO<sub>2</sub> by 10% and duration of exercise by 16%—is similar to or better than the effect on exercise demonstrated in most drug studies. In this study of biventricular pacing, similar increases in peak measures of exercise were observed in patients who were already receiving maximal medical therapy.

The effect of increase in peak VO<sub>2</sub> was independent of HR response, as shown by the significant increase in O<sub>2</sub> pulse (VO<sub>2</sub>/HR). The O<sub>2</sub> pulse in this patient group was lower than in normal subjects (normal ~15 ml/beat), as would be expected in a group of patients with advanced HF (14). Exercise capacity is reduced in HF patients not only

because of a decreased cardiac output response on exercise leading to tissue hypoxia, which results in premature lactate mediated metabolic acidosis, but also because of additional peripheral adaptations leading to poor uptake of oxygen into tissues (26). The increase in O<sub>2</sub> pulse may be a result of a higher stroke volume and/or improved uptake and utilization of oxygen in the skeletal muscle beds. Each phase of the trial lasted only three months, making it more likely that the improvement observed with biventricular pacing was related to an increase in stroke volume rather than to an increase in peripheral oxygen extraction, which implies major changes in the skeletal muscle characteristics and generally takes longer. This would be consistent with the increase in stroke volume observed with biventricular pacing in acute pacing studies (8,27). Improved cardiac function with biventricular pacing has been shown to be at diminished energy cost in contrast to inotropic agents (28). We included all patients in

**Table 2.** Measures of Submaximal Exercise During Inactive and Active Pacing in Each Patient

Pt	Inactive		Active	
	AT as % Maximum Predicted VO <sub>2</sub>	6-Min Walk, m	AT as % Maximum Predicted VO <sub>2</sub>	6-Min Walk, m
1	20	197	21	370
2	38	305	35	319
3	41	414	51	468
4	34	305	34	257
5	nd	153	25	212
6	26	207	32	474
7	49	470	48	467
8	nd	388	nd	393
9	50	351	50	369
10	28	188	67	442
11	48	366	54	448
12	34	363	39	405
13	48	355	42	365
14	28	351	31	400
15	32	438	44	477
16	49	327	71	332
17	35	380	71	542
18	31	428	47	456
19	45	570	45	670
20	25	435	26	423
21	32	330	54	291
22	36	391	50	517
23	48	324	63	392
24	24	346	25	328
25	44	305	55	318
26	46	412	58	469
27	38	361	41	478
28	39	403	22	403
29	38	550	55	550
30	33	377	26	402
Mean	37	359	44	414
p value			0.002	0.001

AT = anaerobic threshold; nd = not determinable; Pt = patient.

the analysis of O<sub>2</sub> pulse regardless of whether chronotropic incompetence was present, because chronotropic incompetence is one of the mechanisms of functional limitation in HF (29).

**Submaximal measures of exercise.** An important aim of treatment for severe HF is to increase the ability of the patient to perform the routine tasks of daily living, such as walking and climbing stairs. Patients with advanced HF perform a series of submaximal exercise tasks during normal daily activity, and measures that reflect such activity may be more useful than contrived exercise tasks in assessing the efficacy of treatment. Improvements in submaximal indices were seen with active pacing for three months: AT increased 18%, 6-min walk distance increased 15%, and VE/VCO<sub>2</sub> slope decreased 11%.

The AT provides a measure of the adequacy of cardiovascular function in response to an exercise stimulus (30). Improvement in AT was observed in 82% of patients with biventricular pacing. Notably, without pacing the AT was not greater than 50% of predicted peak VO<sub>2</sub> in any patient, but this threshold was exceeded in 12 patients with pacing.

This may be of particular benefit in reducing muscular fatigue, which has been demonstrated to be an important determinant of exercise limitation in HF (26).

The 6-min walk test is another measure of submaximal exercise capacity. Although it provides no information for assessing the mechanism of exercise limitation, it is a simple and reproducible indicator of ability to perform tasks of daily living shown to be particularly useful in the assessment of treatments—for example, in the Studies of Left Ventricular Dysfunction (SOLVD) trial (31). With active pacing in patients considered to be receiving optimal pharmacologic therapy, there was an additional increase in walk distance similar to the improvement in metabolic gas exchange indices of exercise capacity, which correlated with improvement in QOL.

The VE/VCO<sub>2</sub> provides a non-invasive assessment of the appropriateness or efficiency of VE (tidal volume × respiratory rate/min) during exercise, and it may contain prognostic information that extends beyond that of peak VO<sub>2</sub> (12,13). In normal subjects the VE/VCO<sub>2</sub> slope is <30 in the region below the AT (14). In HF this slope is generally increased, implying increased ventilatory drive, and this was observed in our patient group. However, biventricular pacing normalized the VE/VCO<sub>2</sub> slope during exercise in 59% of the patients receiving optimized medical therapy for HF. The slope of VE/VCO<sub>2</sub> is determined by two factors: 1) behavior of arterial CO<sub>2</sub> tension during exercise and 2) the fraction of tidal volume, V<sub>t</sub>, that goes into dead space, V<sub>d</sub>. The mechanisms responsible for exercise hyperpnea have not yet been fully elucidated. Current information suggests that a major source for a steep VE/VCO<sub>2</sub> slope in congestive HF is increased non-uniformity of ventilation perfusion (V/Q) causing inefficient gas exchange, although many other factors may cause the increased ventilatory response to exercise of patients with HF (32,33). Biventricular pacing increases cardiac output (8) and reduces left atrial pressure (27) leading to less pulmonary congestion, which may lead to improved ventilation perfusion matching. Such changes would be expected to reduce ventilation perfusion mismatch and may account for the dramatic improvement in ventilatory drive observed with biventricular pacing.

**Study limitations.** Peak exercise time during a progressively loaded test is dependent on motivation from the patient and investigator. The design of this study, with each patient being his/her own control and being blinded to the mode of pacing, attempted to counter any effect of motivation. Because this was a multicenter study, not all exercise tests had all indices available—hence, the reduction in numbers from those enrolled to those finally included. The follow-up period for this study was relatively short.

## CONCLUSIONS

Biventricular pacing can significantly improve both maximal and submaximal measures of exercise, which may better reflect exercise capacity during normal daily activities. The

increased ventilatory drive of patients with HF was reduced with biventricular pacing. Changes observed were consistent with improvements in QOL. Biventricular pacing is a potentially useful therapy for patients with severe HF and intraventricular conduction delay.

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